RECEIVED
CENTRAL FAX CENTER
NOV 2 8 2007

REMARKS

Arguments rebutting the rejections of claims 44-67 accompanied the filing of a Request for Continued Examination pursuant to 37 CFR § 1.114 on October 29, 2007. No additional arguments concerning these claims are made below. New claims 92-115 cover essentially the same subject matter as cancelled claims 68-91, although they are not identical. The rejections of claims 68-91 articulated in the Office Action dated October 5, 2007 (hereinafter, the Office Action), as they would apply to new claims 92-115, are addressed below.

Rejections under 35 USC § 103

Claims 68-91 were rejected as obvious over US Patent No. 6,673,575 (hereinafter, Franze). The Office Action states:

> It would have been obvious at the time the invention was made to make media and use it for controlling the sialation [sic] of protein (particularly recombinant) by cells (particularly CHO) in culture wherein the media contains fructose, mannose, galactose, and any combinations thereof as a matter of routine experimentation for the optimizing of sialation [sic] control. The depth of the prior art is significant and clearly it has established that the selection of sugar, amounts thereof and other normal culture parameters are result effective variables.

Office Action, page 4.

Graham Analysis

The Remarks section of the submission filed October 29, 2007 with the Request for Continued Application contained an extensive analysis under *Graham v. Deere*, 148 USPQ 459 (S.Ct. 1966). Please incorporate the subsections concerning the scope and content of the prior art (pages 7-10) and the level of skill in the art (page 12) herein. The differences between the cited references and claims 92-115 are pointed out below, and the *Graham* factors are weighed.

Differences Between the Claims and the Cited References

If only references utilizing CHO cells are applied, no relevant reference has been cited against claims 92-115. Only Franze has been cited against these claims, and, as explained below and in the submission dated October 29, 2007, data has been submitted

that indicates that the methods of Franze do not lead to increases in protein sialylation in CHO cells. Kadoya et al., submitted with the IDS dated October 29, 2007. Although Franze does recite CHO cells as part of a list of potentially usable cell types (col. 4, lines 39-58), the data in Franze is generated using human cells. Proprietor's Observations, English translation, page 8, submitted with the IDS dated October 29, 2007. Thus, Franze recites a genus of cells types, whereas claims 92-115 select a single species from this genus, that is, CHO cells. The data in Kadoya et al. (*supra*), which describes an attempt to reproduce the data in Franze in CHO cells, indicates that the methods described in Franze do not increase protein sialylation in CHO cells. In the pending opposition against EP 1 036 179, which is the European counterpart of Franze, the patentee has limited all claims to human cells. See Proprietor's Observations, throughout, and including the Main and Auxiliary Requests. Moreover, the patentee has agreed that "in the experiments of D12 [Kadoya et al.] using CHO-cells, no improvement can be found." Proprietor's Observations, page 8. Thus, even the patentee has taken a position that the methods of Franze are without effect in CHO cells. Therefore, the disclosure of Franze cannot reasonably extended to include CHO cells, and Applicant asserts that the recitation of CHO cells in claims 92-115 distinguishes these claims from Franze.

There are further differences between Franze and the claims 92-115. First, the specific combinations of (1) fructose and galactose and (2) fructose, galactose, and mannose are not pointed to in Franze. Instead, Franze discloses a broad genus including all carbohydrates and all combinations thereof. Franze, col. 2-3, lines 64-3. Subgenera called out by Franze include all monosaccharides and disaccharides and all combinations thereof (estimated to include more than 8.8×10^{12} different combinations in Applicant's response of April 10, 2006) and eleven specific sugars and all combinations thereof (calculated to include 2047 different combinations of from one to eleven sugars in Applicant's response dated April 10, 2006). Franze, col. 3, lines 4-9. Thus, Franze discloses a broad genus of carbohydrates and combinations thereof, whereas claims 92-115 recite two species selected from this genus.

Weighing of the Graham Factors

Claims 92-115 are nonobvious over Franze for several reasons. First, Applicant submits that Franze is not a relevant reference because claims 92-115 are limited to media and methods for CHO cells and the methods of Franze have been demonstrated to be inoperative in CHO cells. *See* Kadoya et al. and Proprietor's Observations. Second, even if Franze is considered a relevant reference, the selection of two, particular combinations of carbohydrates from the huge genus of combinations disclosed in Franze is nonobvious. Third, as discussed in the submission dated October 29, 2007, the art of cell culture is unpredictable, and there was no reasonable expectation that sialylation of a protein produced by CHO cells would be increased by the addition of mannose, fructose, and galactose or of galactose and fructose to a medium.

Such a lack of expectation of success was supported by teach away references such as Nyberg (Ph.D. Thesis, MIT, 1998, of record), which demonstrates that addition of mannose, galactose, fructose, or a combination of galactose and mannose to medium does not affect N-glycan site occupancy of interferon gamma produced by CHO cells. Nyberg, Figure 6.2 and page 166. Site occupancy is related to sialylation in that there must be a glycan attached to an N-glycan site for the N-glycan to be sialylated. Baker et al. (Biotechnol. Bioeng. 73: 188-202 (2001), of record) showed that adding biosynthetic precursors of protein sialylation to a culture did not necessarily lead to increases in protein sialylation. Baker et al., p. 194-196 and Table III. Specifically, adding glucosamine, a sialic acid precursor, plus uridine to cultures of NSO or CHO cells led to a moderate or a pronounced decrease in protein sialylation, respectively. Baker et al., Table III, page 194 and page 196. Thus, both Nyberg and Baker et al. teach away from the claimed invention, leading to a lack of expectation of success.

Such a lack of expectation of success is further supported by the Declaration under 37 CFR § 1.132 of Dr. Carole Heath (submitted December 20, 2006; hereinafter, the Heath Declaration). The Heath Declaration states that one of skill the art "would be able to read, understand, and evaluate scientific publications." Heath Declaration, page 1. This being the case and given the description in Examples 5 and 7 of Franze, one of skill in the art could not come to an unambiguous conclusion as to which experimental factor was responsible fro the observed results in Examples 5 and 7. Heath Declaration,

pages 2-4. Therefore, one of skill in the art would not have a reasonable expectation that the addition of one or more carbohydrates to a medium would increase protein sialylation. The Heath Declaration also states that one of skill in the art would not expect all monosaccharides and dissacharides to be interchangeable in a cell culture process. Heath Declaration, page 4. Based on the teachings of Franze, "one of skill in the art could not reasonably believe that adding any two or more monosaccharides or disaccharides to a cell culture would necessarily increase glycosylation." Heath Declaration, page 5. Thus, one of skill in the art would lack a reasonable expectation of success. Therefore, Applicant submits that claims 92-115 are nonobvious and requests allowance of these claims.

Rationales to Support Obviousness Post-KSR

To support a rejection under a rationale that prior art elements have been combined according to known methods to yield predictable results, the following findings must be articulated: 1) the prior art included all elements claimed; 2) one of ordinary skill in the art could have combined the elements as claimed by known methods, and each element would perform the same function it did separately; 3) one of skill in the art would recognize that the results of the combination were predictable; and 4) any other finding believed to be necessary under *Graham*. 72 FR § 57528-57535. Further, when an applicant challenges an unsupported factual assertion by an examiner, the examiner should support the factual assertion with objective evidence. *Ex parte Natale*, 11 USPQ2d 1222 (Bd.Pat.App.&Interf. 1989). Failure to do so is reversible error. *Id.* As explained below, Applicant asserts that the rejection of claims 68-91 is improper because the required findings have not been articulated, and, even if they had been, Applicant has submitted objective evidence showing that the required findings could not be properly substantiated.

With regard to the first required finding, i.e., that the prior art included all claim elements, the only reference cited against claims 68-91 is Franze. Franze discloses the sugars galactose, mannose, and fructose as members of a large genus and mentions CHO cells as part of a list of cell types. Franze, col. 3, lines 4-20 and col. 4, lines 39-50. The pending claims in the instant application are now limited to media and methods for CHO cells. As explained above, the methods of Franze have been demonstrated to be

inoperative in CHO cells, and Applicant therefore submits that Franze cannot be interpreted to disclose a method that can be used in CHO cells. Thus, Applicant submits that Franze does not include all claim elements and that the required finding could not be properly substantiated.

With regard to the second required finding (that one of ordinary skill in the art could have combined the elements as claimed by known methods, and each element would perform the same function it did separately), Applicant asserts that the required finding has not been articulated in the Office Action and could not be properly substantiated if it had been. The separate effect of each recited sugar, that is, galactose, mannose, and fructose, on sialylation of a protein produced by CHO cells is not demonstrated by any cited reference. Franze, the only reference cited against claims 68-91, does not teach the effects of galactose, mannose, or fructose, as single medium additives, on protein glycosylation in mammalian cells or in CHO cells. Thus, the separate functions of these elements were not known based on Franze, and one of skill in the art would be without any basis for determining whether each element performed as it did separately.

Furthermore, data in the instant application show that the sugars recited in claims 92-115 do not have the effects that they had separately because their effects are not additive. Specification, Example 1, Figure 2. For example, fructose had no effect as a single additive and galactose led to a slight increase. The combination of galactose and fructose produced a greater increase in sialylation than did galactose alone. Specification, Figure 2. Similarly, if the effects of mannose (modest decrease), galactose (modest increase), and fructose (no effect) on sialylation were added, one would expect only a very slight increase. Instead, a substantial increase is observed with combination of galactose, fructose, and mannose. Specification, Figure 2. Therefore, each sugar recited in the claims is shown not to be performing the same function that it performed separately. Thus, even if the Office Action had articulated the second required finding, this finding could not be properly substantiated. Claims 92-115 are therefore nonobvious.

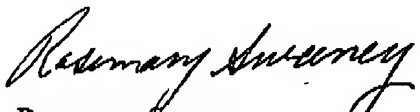
With regard to the third required finding, i.e., that one of skill in the art would recognize that the results of the combination were predictable, this finding is also not

articulated in the Office Action and Applicant has offered evidence showing that such a finding is not supportable. Applicant asserts that one of skill in the art would not recognize that the results of the combination were predictable based on the following evidence. The Heath Declaration explains that the experiments described in Franze do not describe controls that would allow one to reasonably make conclusions about which experimental parameter was responsible for the observed results. Heath Declaration, pages 2-4. Further, one of skill in the art would not suppose that any and all monosaccharides and dissacharides were interchangeable in a cell culture process. Heath Declaration, page 4. Thus, one of skill in the art could not predict based on the results of Franze with the combination of glucose, galactose, and mannose in human cells that the addition of any different combination of mono- or disaccharides to a medium could increase protein sialylation in any and all cells types. Indeed, data in the instant application shows that addition of some carbohydrates and combinations of carbohydrates does not lead to increases in protein sialylation, and the data of Kadoya et al. shows that the methods of Franze are not operable in CHO cells. Moreover, as explained above, there is a lack of expectation of success. Therefore, the third required finding could not be substantiated even if it had been articulated. Therefore, claims 92-115 are nonobvious.

Conclusion

Applicant submits that all claims are in condition for allowance and respectfully requests notice to that effect. Should the Examiner believe that any outstanding issues could be most easily resolved via teleconference, he is invited to contact the undersigned at the direct dial number given below.

Respectfully submitted,



Rosemary Sweeney
Attorney/Agent for Applicant
Registration No. 52,264
Phone: 206-265-7817
Date: November 28, 2007